CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

MEDICAL REVIEW(S)

DEC 1 1999

Medical Officer's Review of NDA 20-965, AZ Submission

Correspondence date: 10/01/99
HFD540 #: 994278
Document ID: AZ

CDER Stamp date: 10/04/99
Review date: 11/22/99

SPONSOR: DUSA Pharmaceuticals

DRUG: LEVULAN KERASTICK (aminolevulinic acid HCl) for Topical Solution, 20% (LEVULAN)

PHARMACOLOGIC CATEGORY: Anti-neoplastic photosensitizer

PROPOSED INDICATION: Treatment of actinic keratoses (AKs) of the face or scalp

DOSAGE FORM/ROUTE OF ADMINISTRATION: Solution, applied topically to actinic keratosis lesions

BACKGROUND:
On June 27, 1999, Agency notified Sponsor that NDA 20-965 was approvable. Agency informed Sponsor that before approval, satisfactory inspections will be required for all manufacturing and testing facilities, and revised draft labeling must be submitted. Revised draft labelling was submitted as part of this submission and has been reviewed and revised by Agency. Labeling that incorporates Agency revisions of sponsor's draft revised label is appended to the review of this submission.

Four informational needs of clinical relevance were identified:

- Characterization of the potential for dermal irritancy with LEVULAN.
- Characterization of the potential for dermal allergenicity with LEVULAN.
- Characterization of the safety and efficacy of LEVULAN in an additional 70 patients. At least 30 of the additional patients should have Fitzpatrick skin types IV-VI. Follow-up at one year after treatment should be arranged to assess the long term recurrence rate of actinic keratoses that have resolved after treatment.
- Characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the [redacted]

Sponsor was also requested to update the NDA by submitting all safety information pertinent for LEVULAN accumulated since the date of the original NDA submission.

On November 5, 1999, at a meeting of the Dermatologic and Ophthalmic Drug Advisory Committee, several committee members expressed concern that because LEVULAN action may cause oxidative DNA damage, and because treatment with LEVULAN does not always result in permanent, complete clearing of AK lesions, the possibility exists that LEVULAN treatment may enhance the oncogenic progression of AK lesions that are

not permanently, completely resolved by LEVULAN treatment. Several committee members also expressed interest in having a patient package insert prepared for the drug product. Agency's revision of sponsor's draft patient package insert is appended to this submission review.

AZ SUBMISSION SUMMARY:
Sponsor has committed to characterize the potential for dermal sensitization with LEVULAN and characterize the safety and efficacy of LEVULAN in an additional 70 patients, including patients with Fitzpatrick skin types IV-VI, and to assess the long tem recurrence rate of AK lesions over a 12-month follow-up period. Sponsor has provided a justification for not undertaking a characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the back and arms, and for not undertaking a characterization of the potential for dermal irritancy with LEVULAN. Sponsor has submitted in tabular form safety data from the results of trials that were still ongoing at the time of NDA submission.

- [redacted]

Following the Draft Guidance *Skin Irritation and Sensitization Study (Modified Draize Test),* Sponsor plans a controlled study on LEVULAN [redacted]

[redacted]

Reviewer's Comment:
The outline of the protocol for the [redacted] study is satisfactory, and as outlined would address the informational need to characterize the [redacted] Sponsor is encouraged to submit the final study protocol prior to study initiation.

Sponsor suggests that characterization of the cumulative irritancy of LEVULAN should not be required. The most compelling consideration that such a study is not necessary is that LEVULAN is unique among dermatological drugs in that it would only be applied once or twice to any given skin site. The relevancy of a cumulative irritancy study for such a product is unclear.

- Characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the

Sponsor notes that the drug dose-ranging and light dose-ranging studies that were undertaken to establish the treatment parameters related to LEVULAN use were designed for treatment of AKs of the face or scalp, and may not be optimal for treatment of lesions at other body sites. In particular,

The sponsor states that

Reviewer's Comment:
Because the sponsor makes several compelling arguments that characterization of the safety and efficacy of LEVULAN for treatment of AKs of the is not warranted at this time, withdrawal of the request by Agency for

is appropriate at this time.

- Characterization of the risk of malignant progression of AK lesions that do not undergo complete, permanent clearing after treatment with LEVULAN.

Numerous epidemiologic studies, as well as the clinical experience of dermatologists, have established that AKs are pre-cancerous skin lesions, with a low risk of malignant progression to squamous cell carcinoma of the skin. The theoretical possibility cannot be excluded that LEVULAN-induced oxidative DNA damage may promote the malignant progression of AKs that are incompletely cleared or that recur after LEVULAN treatment. As part of the approval letter, sponsor should be asked to address this possibility by committing to perform a clinical study involving long-term (at least 12 month follow-up) of treated patients. A goal of this study should include characterization of the recurrence rate at 12 months of AK lesions that cleared by the primary endpoint (e.g., 8 weeks). In addition, this study should also characterize the histopathology of AK lesions in long-term follow-up. The following discussion concerning the histopathology of different grades of AK lesions is based on the article "Incipient Intraepidermal Cutaneous Squamous Cell Carcinoma: A Proposal for Reclassifying and Grading Solar (Actinic) Keratoses", by Yantos et al., Semin. Cutan. Med. and Surg., Vol. 18, No. 1, 3/99, pp. 3-14.

All AK lesions are characterized by atypical keratinocytic proliferation in the epidermis. AK lesions that are hypothesized to have undergone comparatively less malignant progression are characterized by atypical keratinocytic proliferation confined to the lower one-third or lower two-thirds of the epidermis. AK lesions that are hypothesized to have undergone comparatively more malignant progression are characterized by atypical keratinocyte proliferation involving the full thickness of the epidermis including adnexal structures. Lesions in which there is extension of neoplastic cells from the epidermis into the papillary or reticular dermis are considered squamous cell carcinoma of the skin. The hypothesis that sponsor's study should be designed to reject is that AK lesions that are (a) completely cleared; (b) completely cleared but recur during follow-up; and (c) not completely cleared carry an increased risk of either (1) atypical keratinocyte proliferation involving the full thickness of the epidermis including adnexal structures, or (2) squamous cell carcinoma of the skin. Sponsor should estimate the spontaneous incidence of progression of actinic keratoses to squamous cell carcinoma of the skin based on a review of the relevant scientific literature, and based on this estimate, should characterize the histopathology of enough treated lesions to preclude the possibility that a clinically significant fraction of completely cleared, completely cleared but recurrent, or not completely cleared lesions undergo malignant progression to full thickness epidermal atypia or to squamous cell carcinoma of the skin as a consequence of treatment.

- Sponsor's update of NDA, with submission of all safety information pertinent for LEVULAN accumulated since the date of the original NDA submission.

Sponsor submitted the safety results from [redacted] ongoing

- Sponsor's literature review relevant to LEVULAN

Sponsor notes the publication of a case report describing a patient believed to have developed contact sensitization from 5-aminolevulinic acid. The patient described in this case report (Gniazdowska et al., Contact Dermatitis, 1998, Vol. 38: 348-349) was receiving photodynamic therapy for Bowen's disease of the vulva. The patient had a positive patch test reaction to 5-aminolevulinic acid. In sponsor's comment on this article, it was noted that the ALA was formulated as a gel rather than a solution, which may have made it more sensitizing, that vulva may be more sensitizing than glabrous skin, and that over 600 patients have been tested by sponsor with a variety of 5-ALA formulations and concentrations, with no reports of contact dermatitis developing in these patients. As mentioned above, sponsor has committed to perform a contact sensitization study of LEVULAN Topical Solution.

REGULATORY CONCLUSIONS

Approvability Issues:

- Sponsor's agreement to the labeling for the drug product and the patient package insert will be required before this application may be approved.
- The theoretical possibility cannot be excluded that LEVULAN-induced oxidative DNA damage may promote the malignant progression of AKs that are incompletely cleared or that recur after treatment. As part of a post-approval commitment, sponsor is requested to address this possibility by committing to perform a clinical study involving long-term (at least 12 month follow-up) of treated patients. A goal of this study should include characterization of the recurrence rate at 12 months of AK lesions that cleared by the primary endpoint (e.g., 8 weeks). In addition, this study should also characterize the histopathology of AK lesions in long-term follow-up. In this regard, the hypothesis that sponsor's study should be designed to reject is that AK lesions that are (a) completely cleared; (b) completely cleared but recur during follow-up; and (c) not completely cleared carry an increased risk of either (1) atypical keratinocyte proliferation involving the full thickness of the epidermis including adnexal structures, or (2) squamous cell carcinoma of the skin. Sponsor should estimate the spontaneous incidence of progression of actinic keratoses to full thickness epidermal atypia or squamous cell carcinoma of the skin based on a review of the relevant scientific literature, and based on this estimate, should characterize the histopathology of enough treated lesions to preclude the possibility that a clinically significant fraction of completely cleared, completely cleared but recurrent, or not completely cleared lesions undergo malignant progression to full thickness epidermal atypia or to squamous cell carcinoma of the skin as a consequence of treatment. Sponsor is encouraged to submit the final study protocol prior to study initiation.

The following comments pertain to the informational needs identified in the June 27, 1999 letter to sponsor, and how sponsor has addressed these needs:

- Characterization of the potential for dermal irritancy and for dermal ~~irritancy~~ allergenicity with LEVULAN KERASTICK (aminolevulinic acid HCl) for Topical Solution, 20%.

/S/

APPEARS THIS WAY
ON ORIGINAL

The outline of the protocol for the skin sensitization study is satisfactory, and as outlined would address the informational need to characterize the potential for dermal sensitization by LEVULAN. Sponsor is encouraged to submit the final study protocol prior to study initiation. The induction phase of the sensitization study, which entails repeated exposures of skin to LEVULAN over a period of several weeks, is de facto a type of dermal irritation study. If sponsor submits to Agency the dermal irritation scores during the induction phase along with data analysis, this may potentially obviate a need for a separate dermal irritancy study.

- Characterization of the safety and efficacy of LEVULAN in an additional 70 patients. At least 30 of the additional patients should have Fitzpatrick skin types IV-VI. Follow-up at one year after treatment should be arranged to assess the long term recurrence rate of actinic keratoses that have resolved after treatment.

Sponsor has agreed to address this informational need. This informational need partly overlaps with the approvability issue relating to characterization of the recurrence rate at 12 months of AK lesions that cleared by the primary endpoint and characterization of the histopathology of AK lesions in long-term follow-up. A single clinical study may potentially address the approvability issue and the informational need.

- Characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the [redacted]

Because the sponsor makes several compelling arguments that characterization of the safety and efficacy of LEVULAN for treatment of AKs of the [redacted] is not warranted at this time, withdrawal of the request by Agency for a commitment to [redacted] is appropriate at this time.

[redacted] 11/22/99

Martin M. Okun, M.D., Ph.D.
Medical Reviewer

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin
HFD-540/Dermatology Team Leader/Walker [redacted] 11/22/99
HFD-540/Medical Reviewer/Okun
HFD-725/Biostatistics Team Leader/Srinivasan [redacted]
HFD-725/Biostatistician/Farr 12/1/99
HFD-880/Biopharm/Noory
HFD-540/Pharm/Nostrandt
HFD-540/Chemistry/Hathaway
HFD-540/Project Manager/Cintron

21 **Page(s) Redacted**

Draft

Labeling

ADDENDUM TO MEDICAL OFFICER'S REVIEW OF NDA# 20-965

JUN 12 1999

Information Reviewed:

1. NDA Amendment, date of submission 3/11/99, CDER stamp date 3/12/99
2. NDA Amendment, date of submission 4/16/99, CDER stamp date 4/19/99
3. NDA Amendment, date of submission 4/26/99, CDER stamp date 4/27/99
4. NDA Amendment, date of submission 4/30/99, CDER stamp date 5/03/99
5. NDA Amendment, date of submission 4/30/99, CDER stamp date 5/03/99
6. NDA Amendment, date of submission 3/31/99, CDER stamp date 4/01/99

Addendum Date: May 08, 1999

Sponsor: DUSA Pharmaceuticals

Proposed trade name: LEVULAN® (aminolevulinic acid HCl) KERASTICK™ for Topical Solution, 20%

DRUG: aminolevulinic acid HCl

PHARMACOLOGIC CATEGORY: Anti-neoplastic photosensitizer

PROPOSED INDICATION: treatment of [redacted] actinic keratoses of the face and scalp

DOSAGE FORM AND ROUTE OF ADMINISTRATION: solution, applied topically to actinic keratoses.

BACKGROUND

Amendments 1 through 6 pertain to: (1) NDA safety update on 19 patients treated under IND [redacted] subsequent to the NDA analyses; (2) labeling update; (3) information requested by medical officer regarding whether lesions on ears were treated; (4) frequency of use of chin rest during light treatment; (5) case report of allergic contact dermatitis resulting from photodynamic therapy with aminolevulinic acid (not the sponsor's formulation); and (6) CVs of unblinded investigators.

AMENDMENTS

1. The only clinical study performed under IND [redacted] since NDA 20-965 was submitted is Protocol ALA-012, "A Phase I/II study of Photodynamic Therapy with Levulan (5-Aminolevulinic Acid HCl) Topical Solution and Visible Red Light for the Removal of Hair". This study has enrolled nineteen patients. Safety information for these patients is now available.

Reviewer's Comment:

- *The adverse event profile among these patients was not substantially different than the adverse event profile seen in the clinical studies submitted to support the indication of treatment of actinic keratoses of the face and scalp.*
- *No deaths or serious adverse events were noted among the nineteen patients.*

2. Sponsor has submitted an amended label replacing "picture text boxes" with digital photographs to show the activation steps of the Levulan Kerastick.

Reviewer's Comment:

- *The digital photographs are acceptable.*

3. Sponsor conducted a review of case report forms for clinical studies ALA-018 and ALA-019 for the purpose of determining the number of target lesions located on patients' ears. Six target lesions were located on the ears, half of which were on patients enrolled in the active arm of the studies. The lesion clearance rate was 67% for ear lesions receiving active treatment and 0% for ear lesions receiving vehicle treatment.

Reviewer's Comment:

- *The number of ear lesions receiving active treatment was too low to permit a reliable estimate of the efficacy of treatment with LEVULAN at this anatomic site. Given that patients with ear lesions were enrolled in the study, it would be appropriate not to exclude ear lesions from treatment in the package label.*

4. For the pivotal Phase 3 clinical trials, sponsor provided to investigators a chin rest designed for patient use during the approximately 16 minute duration of light treatment. It was unclear from sponsor's initial submission whether patients did actually use the provided chin rest. At the request of the medical reviewer, sponsor performed a retrospective evaluation to estimate the percentage of patients who utilized the chin rest supplied by sponsor. Based on responses, more than 50% of the patients in the Phase 3 trials used the chin rest. Sponsor has agreed to include wording for the operating device that states that "A chin rest, available from DUSA, may be used to provide support for the patient's head during treatment." The sponsor is submitted a PMA Amendment providing device design and manufacturing information for the chin rest used in the Phase 3 trials.

Reviewer's Comment:

- *These changes are satisfactory.*

5. This is a case report of a patient who developed allergic contact dermatitis following photodynamic therapy with an aminolevulinic acid solution different than LEVULAN® KERASTICK™. The allergic contact dermatitis resolved with treatment with topical corticosteroids. On patch testing, the patient was found to be reactive to 20% aminolevulinic acid solution.

Reviewer's Comment:

- *This case report points out the need for dermal sensitization studies with LEVULAN®, which have not yet been performed.*

6. This is a listing of the curriculum vita of all unblinded investigators in the two pivotal clinical studies, ALA-018 and ALA-019. In these studies, the unblinded investigators interviewed patients to elicit adverse events and characterized the adverse events on the CRFs.

Reviewer's Comment:

- *The information was reviewed.*

/S/

Martin M. Okun, M.D., Ph.D.

cc:
Archival NDA
HFD-540
HFD-540/Division Director/Wilkin /S/ 5/21/99
HFD-540/Dermatology Team Leader/Walker
HFD-540/Medical Reviewer/Okun
HFD-540/Project Manager/Cintron /S/ 6/12/99

APPEARS THIS WAY
ON ORIGINAL

Medical Officer's Review of NDA 20-965

APR 3 1999

1 General Information

1.1 NDA submission number 000

1.2 Applicant identification

1.2.1 *Name*

DUSA Pharmaceuticals, Inc.

1.2.2 *Address and telephone number:*

400 Columbus Avenue
Valhalla, N.Y., 10595

1.2.3 *Name of company official or contact person:*

Samuel D. Swetland
Vice President, Regulatory Affairs and Compliance
Guidelines, Inc.
10320 USA Today Way
Miramar, FL 33025
(Ph.) 954-433-7480; (Fax) 954-432-9015

1.3 Submission/review dates

1.3.1 Date of submission (date of applicant's letter)

June 29, 1998

1.3.2 CDER stamp date

July 01, 1998

1.3.3 Date submission received by reviewer

July 28, 1998

1.3.4 Date review begun

August 11, 1998

1.3.5 Date review completed

April 1, 1999

1.4 Drug identification

1.4.1 Generic name

Aminolevulinic Acid HCl

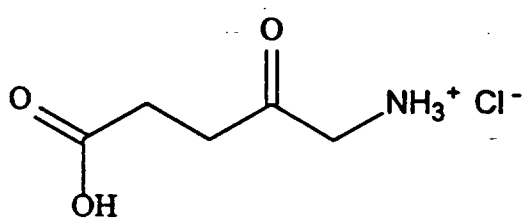
1.4.2 Proposed trade name

LEVULAN® Kerastick™

1.4.3 Chemical name

5-amino-4-oxopentañoic acid

1.4.4 Chemical structure:



1.4.5 Molecular formula

$C_5NO_3H_9$-HCl

1.4.6 Molecular weight

167.59

1.5 Pharmacological Category

Anti-neoplastic photosensitizer

1.6 Dosage Form

Solution

1.7 Route of Administration

Topical

1.8 Proposed Indication & Usage section:

Treatment of actinic keratoses of the face and scalp

1.9 Proposed Dosage & Administration section:

From the proposed label:

1.10 Related Drugs

None

1.11 Material Reviewed

1.11.1 NDA volumes reviewed

NDA Volumes Reviewed and their Contents

Volume	Contents
1.1	Application Summary
1.29	Overview
1.52-1.59	Clinical Study ALA-018
1.60-1.66	Clinical Study ALA-019
1.71	Integrated Summary of Efficacy, Integrated Summary of Safety
1.70	Retrospective Study of Clinical History in Patients with Erythropoietic Protoporphyria and Acute Intermittent Porphyria

1.11.2 Regulatory Documents Reviewed

Minutes of End of Phase 2 meeting, minutes of Pre-NDA meeting.

1.11.3 Non-Regulatory Documents Reviewed

Literature Search on the Epidemiology of Actinic Keratosis

1.12 Regulatory Background

December 1, 1992: Sponsor files IND#

November 4, 1996: End of Phase 2 Meeting, Clinical comments

- Patients will have only one site (either the face or the scalp) treated
- Photographs should be taken to back up investigator's evaluation, and photographs should be taken for each patient that has been retreated at a specific site
- Each center will have a list of investigators who are blinded and unblinded before starting the study
- The primary efficacy criteria is the percentage of patients who have greater than 75% complete response of their lesions
- Pigmentary changes (hypo or hyperpigmentation) are considered adverse events
- Laboratory evaluations will be performed at 4 weeks
- Extent of goggle use should be defined in the protocol
- Sponsor should clarify whether hyperkeratotic lesions are target lesions

2 Table of Contents

3 Chemistry/Manufacturing Controls

See Dr. J.S. Hathaway's Review (unavailable when Medical Officer Review was completed).

4 Animal Pharmacology/Toxicology

See Dr. A. Nostrandt's Review of Pharmacology and Toxicology Data for more detail.

Sponsor has characterized the toxicological profiles of aminolevulinic acid and of pyrazine 2,5-dipropionic acid, a condensation product present at low levels in LEVULAN®. For both chemicals, the human equivalent dose of the no observed effects level in preclinical studies exceeded by several orders of magnitude the expected human dose (7-15 mg LEVULAN®), whether administered intravenously or intraperitoneally (for aminolevulinic acid), or orally or intraperitoneally (for pyrazine 2,5-dipropionic acid).

Several genotoxicity assays of aminolevulinic acid were performed, which were negative, but protoporphyrin IX (PpIX) formation was not demonstrated in these assay systems, so the possibility that genotoxicity may result from unusually high levels of this metabolite induced by exogenous application of aminolevulinic acid cannot be excluded. Indeed, in one study cited by sponsor, genotoxicity was observed in cultured rat hepatocytes where PpIX formation was documented.

The sponsor has not submitted any studies that assess the effects of LEVULAN® on fertility

Reviewer's Comment: Given the likelihood that ALA is rapidly and quantitatively metabolized to form heme, and that it is an endogenous metabolic intermediary in the heme biosyntheitic pathway, it is highly improbable that LEVULAN® would be teratogenic. Nonetheless, given the absence of preclinical teratogenicity studies, LEVULAN® should be given to a pregnant woman only if clearly indicated.

Only one submitted study examined acute dermal toxicity of the to-be-marketed formulation of LEVULAN® (in rabbits). Examination for dermal irritation revealed dose-related erythema, edema, desquamation, and fissuring. Histologic evidence of dermal inflammation was seen in treated and untreated animals, and was considered unrelated to treatment.

5 Devices

See Dr. R. Feltenn's PMA Review (not availablewhen this review was completed) for evaluation of the light source and other devices used in the pivotal trials.

6 Human Pharmacokinetics/Pharmacodynamics

See Dr. A. Noory's Clinical Pharmacology/Biopharmaceutics Review for more detail.

Mechanism of Action— Synthesis of ALA (by [redacted] is the first step in heme synthesis, which is controlled by a feedback mechanism in which the presence of free heme in cells inhibits the synthesis of ALA. Administration of exogenous ALA bypasses the feedback mechanism and leads to

temporary accumulation of several porphyrin intermediates of the heme biosynthetic pathway, including the photosensitizer protoporphyrin IX (PpIX). Over time, ferrochelatase metabolizes these intermediates to heme.

In photodynamic therapy (PDT), tissue is exposed to wavelengths of light able to penetrate target tissue and activate the phototoxic agent. PpIX absorbs light maximally in the Soret band (400 to 410 nm.). This is the wavelength of visible blue light. It is hypothesized that light of this wavelength excites PpIX to the metastable triplet state, which subsequently decays back to the ground state with concomitant release of fluorescence. This fluorescence excites oxygen to the singlet state, in which form it damages membrane lipids via peroxidation, damages DNA, and causes cell death.

Absorption and Distribution—Sponsor performed a two-way cross-over study of the pharmacokinetics of ALA and PpIX in healthy volunteers after intravenous and oral dosing (Study PK-01). The oral bioavailability of ALA was 50-60%. Over the 24 hours after administration of 128 mg of ALA-HCl (by either route), the mean plasma concentrations of PpIX ranged from zero to 0.042 μg/ml (with a lower limit of quantitation[ ]ng/ml). In comparison, the free erythrocyte protoporphyrin concentration is less than 0.5 μg/ml in normal patients, and ranges from 3 to 45 μg/ml in patients with erythropoietic protoporphyria. Of note, sponsor estimates that 7-15 mg of ALA is administered per actinic keratosis during treatment with the LEVULAN® Kerastick™--much less than what was administered in the cross-over pharmacokinetics study.

Sponsor evaluated the in vitro penetration of [^{14}C]-ALA in the 20% solution used in the pivotal clinical trials into intact and tape stripped human cadaver skin using[ ] Approximately 0.7% of the applied ALA penetrated intact skin at 16 hours, and 29% of the applied ALA penetrated tape stripped skin at 16 hours. Since the stratum corneum of photodamaged or actinic keratosis skin may not have normal barrier function, the latter percentage of penetration may be a more accurate measure of how much ALA penetrates following application to actinic keratosis lesions.

Sponsor also evaluated the pharmacokinetics of ALA-Induced PpIX-associated fluorescence in actinic keratosis and adjacent skin (Pharm-03). For both actinic keratosis and adjacent skin, peak fluorescence intensity was measured at approximately 12 hours after application, with comparable plateau periods, $t_{1/2}$, and peak intensity. These data indicate there is little fluorescence selectivity following LEVULAN® administration to actinic keratosis and adjacent skin sites on the face and scalp—likely because adjacent skin is photo-damaged, with dysfunctional stratum corneum that is not completely effective at serving as a barrier to penetration of topically applied ALA.

7 Human Clinical Experience

7.1 Foreign Experience

The sponsor states that LEVULAN® or other brands of aminolevulinic acid HCl have not been commercially marketed in foreign countries.

7.2 Post-Marketing Experience

There is no post-marketing experience with LEVULAN or aminolevulinic acid, as at this time this drug substance has not been approved for any indication.

8 Clinical Studies

8.1 Introduction

8.1.1 Clinical and Histological Features

R.A. Schwartz describes the clinical appearance of an actinic keratosis (AK):

> A skin-colored to reddish brown or yellowish black ill-defined round or irregularly shaped macule or papule with a dry firmly adherent scale. The actinic keratosis is often better appreciated by palpation than visualization because of its distinctive roughened quality. The AK is usually 1-3 mm in diameter, but varies up to several centimeters. It is usually seen on sun-exposed body regions in persons with many years of solar exposure.(Schwartz, J. of Dermatol. Surg. 23: 1009-1019, 1997).

The clinical appearance of AKs is sufficiently distinctive that biopsy to confirm the diagnosis is rarely necessary; one study revealed that a clinical diagnosis arrived at by experienced dermatologists is confirmed in 94% of cases by histology (Ponsford et al., Aust. J. Dermatol., 24, 79-82, 1983). Histopathology of AK lesions shows that the epidermis is slightly to markedly hyperkeratotic, with a thin granular layer and irregular acanthosis. Lesional keratinocytes are variable in size and shape, with enlarged nuclei and prominent nucleoli. Within AK lesions, hair follicles, sebaceous glands, and apocrine and sweat glands are typically unaltered (perhaps because they are located more deeply within the dermis, and therefore most incident UV light is filtered before reaching these appendages). Following destruction of AK lesions, normal keratinocytes from these appendages are believed to migrate out and replenish the epidermal surface.

8.1.2 Epidemiology

In a cross-sectional epidemiological study with follow-up of randomly chosen subjects aged 60 and older from South Wales, England (Harvey et al, Br. J. Cancer, 74: 1302-1307, 1996), the crude prevalence of AKs was estimated at 23% of examined subjects, with an incidence rate of new AKs at 149 lesions per person-years. These rates probably underestimate the true incidence and prevalence of AKs because older subjects who are less likely to participate in population-based screenings have a higher risk for AKs.

The principal risk factors for the development of AKs include (in descending order of relative importance) pale skin type, age, cumulative sun exposure, and male gender (Harvey et al., Br. J. Cancer, 74: 1308-1312). The risk associated with male gender likely reflects that males may spend more time outdoors without shirts, that feminine hair styles afford more protection from sun exposure, and that males are at greater risk for androgenic alopecia with concomitant loss of natural sun protection. Gender-related differences are more marked for older people. A six month randomized, controlled trial has demonstrated that sunscreen use is associated with only a modest reduction in the number of AK lesions (the mean number of AKs increased by 1 per subject in the base

cream group and decreased by 0.6 per subject in the sunscreen group) (Thompson et al. NEJM, 329: 1147-51, 1993). Also, retrospective studies have revealed that self-reported use of sunscreen does not have a marked protective effect, for several possible reasons: (1) self-reporting is subject to recall bias; (2) most sun damage in elderly patients occurred before effective sunscreens were used widely; (3) sunscreens may not be used properly; (4) confounding caused by the likelihood that those individuals most sensitive to sun damage (light skinned people) are those most likely to use sunscreen.

Longitudinal studies have revealed that AKs can remit spontaneously:

- Marks et al. (Br. J. Derm., 115: 649-655, 1986) reported that after a year of follow-up of 1040 Australians aged 40 or older, the AK regression rate was calculated to be 100 per 1000 AKs per year.
- Harvey et al. (Br. J. Cancer, 74: 1302-1307, 1996) reported that after one to two years of follow-up in Englishmen and women aged 60 and older, the AK regression rate was calculated to be 150 per 1000 AKs per year.

Thus, the natural history of AKs can best be described as continual flux, with new lesions appearing and some old lesions remitting, and with the incidence and remission rates in part dictated by solar exposure.

8.1.3 Indications for treatment

In the reviewer's clinical experience, AKs are often incidental findings detected during routine physical examination, or during an office visit prompted by another dermatological condition. Some patients seek medical treatment for AKs because they are concerned that these are malignancies, or because of cosmetic concerns about the lesions' red or scaly appearance. Although usually asymptomatic, mild lesional tenderness is occasionally reported (Sober et al., Cancer 75: 645-650, 1995). Some patients find the loss of smooth skin texture caused by the presence of AKs very annoying.

The generally accepted standard of care in the United States is for dermatologists to destroy AKs (Feldman, S.R., J. Am. Acad. Dermatol. 1999; 40:43-7). The chief rationale cited to justify the expense and patient discomfort associated with AK destruction is that it preempts their malignant transformation.

8.1.4 Human Studies Submitted in NDA 20-965

The following tables list all human studies submitted in NDA 20-965, with enrollment numbers for study drug and active control.

Studies submitted for NDA 20-965: Clinical Pharmacology Studies

Study No.	Route	Dosage/ Concentration	Design	No. of Patients	Outcome
PK-01	IV/PO	128mg/ 10mL	Single dose, with crossover and one week wash-out, by different routes	6 normal volunteers	PO absorbance 50-60%; PpIX plasma concs. undetectable past 12 hours; No side effects noted
Pharm-03	Topical	20% (w/v) Solution [to-be-marketed formulation] and vehicle	Vehicle controlled, cutaneous PpIX fluorokinetic study in patients with actinic keratoses, on affected and adjacent skin	12 patients	Peak fluorescence intensity at ~12 hours; Little fluorescence selectivity following LEVULAN administration to AK lesions and adjacent skin;

From: Table G.1 Biopharmaceutics Study Summary, Vol 1.1, pp. 145-147

Studies submitted for NDA 20-965: Uncontrolled Clinical Efficacy Study

Study No.	Route	Drug & Light Dosage/ Concentration	Design	No. of Patients	Outcome
ALA-003	Topical	10%, 20%, 30% (w/w) dissolved in emollient cream; Light source: laser (630 nm) at 10-150 J/cm^2	Phase 1, Drug Dose Ranging Study, for treatment of multiple actinic keratoses of the face and body	40	Patients with active treatments (all three arms) had more complete responses than vehicle-treated patients
ALA-003A	Topical	0%, 20%, 30% (w/v) solution, 20% ointment, 20% emollient cream, either O/N or for 3 hours; Light source: BLU417 (non-laser light, 417 nm) 10-20 J/cm^2	Phase 1, Drug Dose Ranging Study, for treatment of multiple actinic keratoses of the face and scalp	12	Overnight application more effective than 3 hour application

Studies submitted for NDA 20-965: Controlled Clinical Efficacy Studies

Study No.	Route	Drug Dosage	Light Dosage	Design	No. of Enrolled Patients	Outcome
ALA-007	Topical	20% (w/v) Solution [to-be-marketed formulation] and vehicle	3 mW/cm^2—2, 5 J/cm^2 5 mW/cm^2—2, 5,10 J/cm^2 10 mW/cm^2—2,5,10 J/cm^2 Light Source: BLU-417	Phase 2, Light Dose Ranging, Investigator Blinded, Vehicle (internally) controlled, treatment of multiple, discrete actinic keratoses of the face and scalp	36	Lesion cure rate better for ALA- than vehicle-treated lesions; Higher light doses more effective; No serious treatment-related AEs
ALA-016	Topical	20% (w/v) Solution [to-be-marketed formulation] and vehicle	3 mW/cm^2—2.5, 5 J/cm^2 5mW/cm^2—2.5, 5, 10 J/cm^2 10 mW/cm^2—2.5, 5, 10 J/cm^2 Light Source: BLU-417 No light, ambient light	Phase 2, Light Dose Ranging, Investigator Blinded, Vehicle controlled, treatment of multiple actinic keratoses and photodamaged skin	43: active/blue light; 10: active/no or ambient light; 11: vehicle/no or ambient light	5W-5J, 5W-10J, 10W-10J were equally effective (patients with 100% complete response rate); No serious treatment-related AEs; Photodamaged skin prone to photosensitization, resulting in more stinging/burning than in ALA-007
ALA-017	Topical	2.5, 5, 10, 20, 30% (w/v) Solutions and vehicle	10 mW/cm^2—10J/cm^2 Light Source: BLU-417	Phase 2, Drug Dose Ranging, Investigator Blinded, Vehicle (internally) controlled, treatment of multiple, discrete actinic keratoses of the face and scalp	124	20%, 30% arms had approximately equal efficacy, superior to 5% arm, which was superior to vehicle arm (patients with 100% complete response rate); No serious treatment-related AEs; Percentage of patients with adverse events (all types) approximately the same in all treatment arms
ALA-018	Topical	20% (w/v) Solution [to-be-marketed formulation] and vehicle	10 mW/cm^2—10J/cm^2 Light Source: 4170 [redacted]	Phase 3, Investigator Blinded, Vehicle controlled, treatment of multiple, discrete actinic keratoses of the face and scalp	88 active, 29 vehicle	Results discussed in section 8.2.1.4
ALA-019	Topical	20% (w/v) Solution [to-be-marketed formulation] and vehicle	10 mW/cm^2—10J/cm^2 Light Source: 4170 [redacted]	Phase 3, Investigator Blinded, Vehicle controlled, treatment of multiple, discrete actinic keratoses of the face and scalp	93 active, 33 vehicle	Results discussed in section 8.2.2.4

8.2 Dermal Toxicity Studies

Sponsor has not performed irritancy, allergenicity, phototoxicity, or photoallergenicity studies on the to-be-marketed formulation. (Phototoxicity testing was performed in ALA-006 with aminolevulinic acid in an ointment formulation). While review of the regulatory history of this drug reveals that there have been no Agency commitments waiving the requirement for these studies, based on the adverse event profile from the two pivotal clinical studies (see below), the reviewer feels there would be little regulatory utility for Agency to require phototoxicity or photoallergenicity studies from sponsor as a Phase 4 commitment. Since it is well-established from the results of the Phase 3 trials that LEVULAN® induces phototoxicity to visible light, reviewer cannot envisage any results from formal phototoxicity or photoallergenicity studies that would have an impact on drug labeling. Also, waiving these studies would spare normal human volunteers the discomfort associated with a phototoxic reaction.

Reviewer's Comment: Allergenicity and irritancy studies should not be waived for the drug product. Sponsor should be encouraged to perform these studies as a Phase 4 commitment. Though aminolevulinic acid is an endogenous metabolic intermediate in the heme synthesis pathway, it is possible that amounts much greater than what is present endogenously, applied to skin with an impaired stratum corneum, may prove irritating. Also, one cannot preclude the possibility that other component(s) of the formulation are irritating or are allergenic. The potential for allergenicity is clinically relevant, as it possible that patients will be exposed repeatedly to LEVULAN® as new AKs develop and are treated.

8.3 Indication #1

Treatment of [redacted] actinic keratoses of the face or the scalp.

8.3.1 Trial #1: ALA-018

8.3.1.1 Objective/Rationale

The objective of this pivotal clinical trial was to assess the safety and efficacy of topical LEVULAN® applied to actinic keratoses lesions, followed by blue light irradiation to the face or scalp, in the treatment of [redacted] (non-hyperkeratotic) actinic keratoses of the face or scalp.

8.3.1.2 Design

This was an eight center, randomized, vehicle-controlled, uneven-parallel clinical trial with blinded investigators (for efficacy assessment) and unblinded investigators (for safety assessment). Different investigators for efficacy and safety assessment were necessary because it was expected that most or all subjects receiving active treatment would experience a characteristic photodynamic response (stinging/ burning, erythema, and edema) during light treatment. If the investigators responsiole for collecting efficacy data knew which patients experienced the photodynamic response, the blind would be broken.

Treatment(s) occurred at Day 0 and at week 8 (if any target lesions that had been treated at Day 0 were persistent at this time point). The last office visit was at week 12. Hence, patients received 12 weeks of follow-up following the first treatment and/or 4 weeks of follow-up following the second treatment. At each treatment, target lesions received two applications of LEVULAN® via dabbing with the KERASTICK® applicator. The primary efficacy variable, defined as the percentage of patients with 100% of target lesions undergoing complete response, was assessed at week 8. Retreatment efficacy was assessed at week 12.

8.3.1.3 Protocol Overview

8.3.1.3.1 Population, procedures

After qualifying for the study, subjects were randomized in a 3:1 ratio to receive a pre-numbered kit containing either LEVULAN® or Vehicle KERASTICK™ applicators. Randomization was done separately for each center in two blocks of 8 and one block of 4.

One hundred seventeen patients were randomized: 88 to receive LEVULAN® and blue light, and 29 to receive vehicle and blue light. Three patients in the LEVULAN® group and one patient in the vehicle group were discontinued from the study. The reasons for discontinuation, as depicted in the following table, were non-compliance with follow-up visits (two LEVULAN® patients, one vehicle patient), and request for withdrawal after LEVULAN® application but less than 500 seconds of blue light application. The reason for this patient's withdrawal was a treatment-related adverse experience ("patient complained it was to[sic] hot in the light"). One patient eligible for retreatment at week 8 (because of persistent target lesion) received drug application but not light treatment.

Patient Discontinuations: ALA-018

Patient Number	Treatment Arm	Reason for Discontinuation	Time of Last Efficacy Measure
18303	LEVULAN®	Patient Non-Compliance	Week 8
18508	LEVULAN®	Patient Non-Compliance	Week 4
18517	LEVULAN®	Patient Requests Withdrawal	None: Patient withdrew at Baseline Visit B (after LEVULAN® applied, with less than 500 seconds of light applied)
18210	Vehicle	Patient Non-Compliance (Patient Lost to Follow-Up)	Week 4
18402	LEVULAN®, Re-treatment	Not specified	Week 12 (Patient did not receive full light dose during retreatment)

INCLUSION CRITERIA

1. Males and non-pregnant female outpatients over the age of 18 years. Females had to be post menopausal, surgically sterile or using a medically acceptable form of birth control, with a negative urine pregnancy test.
2. Presence of a minimum of 4 discrete actinic keratotic lesions on either the face or scalp. However, up to 15 discrete target lesions could be treated, but they had all to be confined to either the face or scalp.
3. Written informed consent.

EXCLUSION CRITERIA

Patients were regarded as non-eligible for the study if any of the following was present:

1. History of cutaneous photosensitization, porphyria, hypersensitivity to porphyrins or photodermatosis.
2. The use of photosensitizing drugs within a time frame where photosensitization from these drugs could still be present.
3. Hyperkeratotic, Grade 3 lesions (very thick and/or hyperkeratotic actinic keratoses) among the targeted lesions.

4. Use of the following systemic or local therapies for the periods specified, prior to entry into the study:
   Within 2 weeks: topical medications, e.g., corticosteroids, alpha-hydroxyacids (glycolic acid, lactic acid) or retinoids (Retin-A®) to the face or scalp.
   Within 4 weeks: systemic steroid therapy
   Within 2 months: cryotherapy to the target lesions, laser resurfacing, chemical peels, topical application of 5-FU or masoprocol (Actinex®) for treatment of actinic keratosis. Systemic therapy with chemotherapeutic agents, psoralens, immunotherapy, retinoids (Tegison®, Accutane®).
5. Any medical condition which, in the opinion of the investigator, could preclude study participation, including renal and hepatic disorders, severe anemia, etc.
6. A known sensitivity to one or more of the Vehicle components (ethyl alcohol, isopropyl alcohol, Laureth 4, polyethylene glycol).
7. Any active infectious diseases.
8. Inherited or acquired coagulation defects.
9. Use of any investigational drug in the previous 30 days.
10. Pregnant or nursing women.
11. Unreliability for the study, including excessive alcohol intake, drug abuse or inability to return for scheduled follow-up visits.

Protocol Synopsis

The clinical protocol calls for the following study visits: screening, two baselines (A and B), follow-up at 24 hours, and at 1, 4, and 8 weeks after treatment. Those patients with persistent target lesions at week 8 have a retreatment visit at week 8, and follow-up visits at 24 hours, at 1 week and 4 weeks after retreatment (i.e. weeks 9 and 12).

Screening Visit: (conducted by unblinded or blinded investigator)

The purposes of this visit are to confirm that the patient satisfies inclusion and exclusion criteria, to collect blood and urine for laboratory testing, and to instruct the patient to return to the site for Baseline Visit A "with appropriate light protective clothing."

Reviewer's Comment: Neither the body of the protocol nor the Appendices elaborate on what sponsor considers "light protective clothing". Also, there is no specific mention in the informed consent form of the necessity of wearing light protective clothing following LEVULAN® application.

Baseline Visit A: (conducted within 2 weeks after screening), (conducted by unblinded **and** blinded investigators)

The purposes of this visit are to select and grade the target lesions, according to the following scale:

Actinic Keratosis Lesion Thickness	
Grade	Description
0	No lesion is palpable or visible
1	Lesions are slightly palpable, and better felt than seen
2	Moderately thick actinic keratoses, easily seen and felt
3	Very thick and/or hyperkeratotic actinic keratoses

To record permanently the identity and location of the four target lesions, a [redacted] derived template was placed over the patients' face and scalp, and the locations of the target lesions were marked on the [redacted] with permanent markers by the blinded investigator. The patients were then randomized to receive either LEVULAN® or vehicle by the unblinded investigator, who subsequently applied the study medication in the following manner::

- Holding the Kerastick™ applicator upright, the investigator crushes the bottom ampule (releasing the hydroalcoholic solution), then crushes the top ampule (releasing the powder [or in the case of vehicle, releasing nothing]), then shakes the applicator for three minutes. The applicator tip should be applied immediately after admixture.
- The tip is pressed against a gauze pad at least twice to ensure that the applicator tip of the is completely moistened.
- The target lesions are gently dabbed with the applicator tip in a manner such that the entire lesion, including the margins, are completely wetted.
- Once the original application has dried, the target lesions are wetted again as described above, for a total of two applications.

The protocol states that investigators should warn patients that during the period between Baseline Visits A and B, the patients should protect the lesions being treated from light exposure for a minimum of 14 to 18 hours after application (i.e. "to avoid direct exposure of target sites to sunlight or other high intensity light sources, including tanning light devices"), and not to wash the treated areas during this time period.

Reviewer's Comment: These instructions are ambiguous and could expose patients to phototoxicity, because the meaning of the term "direct exposure" is not clear. Labeling instructions should say: "avoid exposure of target sites to sunlight or other sources of bright light."

Baseline Visit B: (conducted within 14 to 18 hours after Baseline Visit A), (conducted by unblinded investigator)

The purposes of this visit are to: (1) evaluate patients for any erythema or edema at the target lesions, or any other signs/symptoms of phototoxicity prior to light treatment; (2) irradiate LEVULAN® or vehicle-exposed lesions with blue light emanating from the 4170 Blue Light Photodynamic Therapy Illuminator (the Illuminator); (3) evaluate patients for burning/stinging during the light treatment; and (4) evaluate patients for any erythema or edema at the target lesions, or any other signs/symptoms of phototoxicity after light treatment.

Prior to the light treatment, the target lesions are gently rinsed off with water and patted dry. The Illuminator is warmed up for 5 minutes (the patient is not present during the warm-up period), and power output is checked to lie between 9 and 11 mW/cm^2 with the DUSA. During light treatment, both patient and medical personnel wear protective eyewear, supplied by sponsor, designed specifically for use with the Illuminator.

For patients with facial lesions:

- The Illuminator is positioned so that the base is slightly above the patient's shoulders, parallel to the patient's face.
- The chin rest supplied by sponsor may be used to provide support for the patient during treatment.
- The Illuminator is positioned around the patient's head so the entire surface area to be treated lies between 2" and 4" from the Illuminator surface:
  - The patient's nose should be no closer than 2" from the surface;
  - The patient's forehead and cheeks should be no further than 4" from the surface;
  - The sides of the patient's face and the patient's ears should be no closer than 2" from the Illuminator surface.

For patients with scalp lesions:

- The knobs on either side of the Illuminator are loosened and the Illuminator is rotated to a horizontal position.
- The chin rest supplied by sponsor may be used to provide support for the patient during treatment.
- The Illuminator is positioned around the patient's head so the entire surface area to be treated lies between 2" and 4" from the Illuminator surface:
  - The patient's scalp should be no closer than 2" from the surface;
  - The patient's scalp and cheeks should be no further than 4" from the surface;
  - The sides of the patient's face and the patient's ears should be no closer than 2" from the Illuminator surface.

Follow-up Visits 2,3,4,5: (24 hours, Weeks 1, 4, 8) (conducted by unblinded investigator, with the blinded investigator assessing efficacy at Weeks 4 and 8).

The purposes of these visits are to: (1) evaluate patients for any erythema or edema at the target lesions, or any other signs/symptoms of phototoxicity or adverse events (at all visits, by unblinded investigator); (2) collect blood and urine for laboratory testing (at 24 hours and 8 Weeks [if retreatment is necessary], by unblinded investigator); (3) photograph the target lesions (at 24 hours, Weeks 4 and 8, by unblinded investigator); (4) assess the clinical efficacy, the cosmetic response, and the pigmentary response (at Weeks 4 and 8, by blinded investigator).

Those subjects with any persistent target lesions at Week 8 were eligible for retreatment of those lesions at that time, following the same protocol as described above. Subjects received LEVULAN® or vehicle application on Follow-up Visit 5. Those subjects who had been randomized to the LEVULAN® arm, who had persistent lesions at Follow-Up Visit 5, received another LEVULAN® application and blue light treatment at this follow-up visit; those subjects who had been randomized to the vehicle arm, who had persistent lesions at Follow-Up Visit 5, received another vehicle application and blue light treatment at this follow-up visit.

Follow-up Visits 6,7,8: [14-18 hours after LEVULAN®/Vehicle application, 24 hours after light application, 1 week after LEVULAN®/Vehicle application (Week 9)] (conducted by unblinded investigator).

These visits have the identical purposes as Baseline Visit B, Follow-up Visits 2 and 3, respectively (see above).

Follow-Up Visit 9: (Week 12) (conducted by unblinded **and** blinded investigators).

The purposes of this visit are to: (1) evaluate patients for any erythema or edema at the target lesions, or any other signs/symptoms of phototoxicity or adverse events (by unblinded investigator); (2) photograph the target lesions; (3) assess the clinical efficacy, the cosmetic response, and the pigmentary response (by blinded investigator); and (4) evaluate patient acceptance of the therapy.

Safety Reporting

Safety assessments were made by the unblinded investigator at each visit. These included a review of adverse events, PDT response (erythema, edema, burning/stinging, wheal, vesiculation, hemorrhage, ulceration, necrosis, erosion, scaling, crusting and itching), pigmentary changes and changes in laboratory parameters.

Adverse Event Reporting

The patient was instructed by the investigator to report the occurrence of any adverse events that occurred during the study. The investigator asked the patient at each visit, in a generalized fashion, regarding any change in their overall condition since the previous visit.

All adverse events were summarized using the COSTART dictionary by body system, and by severity.

PDT Response

As mentioned in the Protocol Synopsis section, overall safety assessment and evaluation of PDT responses at the treatment sites were made at each visit. Objective assessments were made by the unblinded investigator and subjective assessments by the patient. These assessments were made prior to LEVULAN or Vehicle application **(Baseline Visit A)**, before and immediately post PDT **(Baseline Visit B)** and at each subsequent visit **(Follow-up Visits 2 through 9)**.

The target lesions were globally evaluated for two of the objective clinical signs of phototoxicity, erythema and edema, using the following scales:

Global Evaluation of Erythema Scale	
GRADE	DEGREE OF ERYTHEMA
0	No lesions exhibit erythema
1	< 50% of the lesions exhibit erythema
2	≥ 50% of the lesions exhibit erythema
3	All lesions exhibit erythema

Global Evaluation of Edema Scale	
GRADE	DEGREE OF EDEMA
0	No lesions exhibit edema
1	< 50% of the lesions exhibit edema
2	≥ 50% of the lesions exhibit edema
3	All lesions exhibit edema

Additional signs of phototoxicity (weal, vesiculation, hemorrhage, ulceration, necrosis, erosion, scaling, crusting and itching), if present, were also recorded on the photodynamic response form of the CRF.

Subjective Assessments

Before, during (at minutes 1, 6, and 11 of treatment), immediately post- PDT, and at each subsequent visit, the patient reported the degree of burning/stinging at the treated sites, using the following scale:

Severity of Burning/Stinging Scale	
GRADE	DEGREE OF STINGING/BURNING
0	None
1	Minimal, barely perceptible
2	Moderate
3	Severe

If stinging/burning was present, the patient was asked about the relative number of lesions affected and the response was graded using the following scale:

Extent of Burning/Stinging Scale	
GRADE	EXTENT OF STINGING/BURNING
1	< 50% of the lesions exhibit stinging/burning
2	≥ 50% of the lesions exhibit stinging/burning
3	All lesions exhibit stinging/burning.

Pigmentary Changes
Pigmentation of the individual lesions was evaluated by both the unblinded and blinded investigators at Baseline Visit A. Pigmentary changes were evaluated by the blinded investigator at Follow-up Visits 3, 4, and 9 (Weeks 4, 8 and 12). The changes were evaluated as hypo- or hyper-pigmented.

Laboratory Evaluations
Blood and urine were collected for laboratory evaluation [for first treatment, at the screening visit and Follow-up visit 2 (24 hours after light treatment); for retreatment, at Follow-up visit 5 (Week 8 visit) and Follow-up visit 7 (24 hours after light treatment)]. The following laboratory evaluations were performed: hemoglobin, hematocrit, full blood count, including white cell differential and platelet count, SGOT, SGPT, LDH, alkaline phosphatase, bilirubin, BUN, creatinine, serum glucose, uric acid, serum electrolytes (potassium, sodium, chloride, bicarbonate), urinalysis, urine ALA, urine HCG for women of child bearing potential (Screening and Follow-up Visit 5, if retreatment was necessary).

8.3.1.3.2 Evaluability criteria

The data sets analyzed by the sponsor consisted of (a) evaluable patients as per protocol (efficacy) and (b) all patients who received treatment (intent-to-treat) [all patients who were enrolled in the study, satisfied admission criteria as specified in the protocol, and all were randomized and received treatment].

Reviewer's primary analysis of efficacy was based on an intent-to-treat approach. Intent-to-treat analysis of the primary efficacy variable (identified in the following section) were

performed at Weeks 8 and 12 with last observation carried forward for those patients with missing data to assess the effects of withdrawals or missing data.

8.3.1.3.3 Endpoints defined (clinical & microbiology)

The primary efficacy variable was based on the complete clearing of the lesions at Week 8. Lesions were designated as cleared (complete response, CR) if "the lesion had completely cleared and adherent scaling plaques of actinic keratoses were no longer evident on the surface of the treated skin when palpated. (Vol. 1.53, pg. 7-7459)." The population evaluated was the I.T.T. population, L.O.C.F. to week 8. Lesion counts were performed by the blinded investigator at baseline and at Weeks 4, 8 and 12. The lesion counts were evaluated by the sponsor as the percent reduction and the percentage of patients with 75% or greater reduction in lesion count as compared to baseline.
Additional analyses (requested by Agency) included the proportion of patients considered a success (complete clearing) in the treatment group compared to the proportion of patients considered a success in the vehicle group.
The secondary efficacy variables include cosmetic evaluations by the investigator and patient and assessment of patient acceptability of this therapy compared to other therapies for actinic keratosis.

8.3.1.3.4 Statistical considerations

Comparability of the two treatment groups with respect to demographic and baseline characteristics was assessed using univariate analysis of variance (ANOVA), with treatment effect for continuous variables and the Cochran-Mantel-Haenszel (CMH) test for discrete variables. Efficacy data was also stratified by center.

8.3.1.4 Study Results

8.3.1.4.1 Demographics, Evaluability

Summary of Baseline Demographic and Disease Characteristics: ALA-018

Characteristic	LEVULAN® (N=88)	Vehicle (N=29)	Overall (N=117)	p-value[a]
Age (years)				
N	88	29	117	0.197
Mean (SD)	67.1 (9.7)	64.2 (12.4)	66.4 (10.4)	
Range	34 – 87	44 – 85	34 – 87	
Sex				
Female	15 (17%)	4 (14%)	19 (16%)	0.944
Male	73 (83%)	25 (86%)	98 (84%)	
Skin Type[b]				
I	19 (22%)	9 (31%)	28 (24%)	0.823
II	46 (52%)	10 (34%)	56 (48%)	
III	21 (24%)	9 (31%)	30 (26%)	
IV	2 (2%)	1 (3%)	3 (3%)	
Race				
White	88 (100%)	29 (100%)	117 (100%)	
No. of Lesions				
4-7	58 (66%)	17 (59%)	75 (64%)	0.620
8-11	19 (22%)	9 (31%)	28 (24%)	
12-15	11 (13%)	3 (10%)	14 (12%)	
Location				
Face	72 (82%)	21 (72%)	93 (79%)	0.225
Scalp	16 (18%)	8 (28%)	24 (21%)	
Lesions	N=615	N=203	N=818	
Lesion Grade				
0[b]	0 (0%)	0 (0%)	0 (0%)	0.666
1	333 (54%)	115 (57%)	448 (55%)	
2	282 (46%)	88 (43%)	370 (45%)	
3[b]	0 (0%)	0 (0%)	0 (0%)	
Pigmentation				
0	537 (87%)	165 (81%)	702 (86%)	0.191
1	75 (12%)	37 (18%)	112 (14%)	
2	3 (0%)	1 (0%)	4 (0%)	

Note: Percentages were calculated based on the number of patients with non-missing values in each treatment group.

[a] P-value is based on ANOVA with treatment for age and Cochran-Mantel-Haenszel general association test for sex and skin type.

[b] Skin Type:

I: White; always burns easily; shows no immediate pigment darkening reaction (IPD); never tans.
II: White; always burns easily; trace IPD; tans minimally and with difficulty.
III: White; burns minimally; IPD+; tans gradually and uniformly (light brown).
IV: Light brown; burns minimally; IPD++; always tans well (moderate brown).
V: Brown; rarely burns; IPD+++; tans profusely (dark brown).
VI: Dark brown or black; never burns; IPD+++; tans profusely (black).

Source: Tables 11.2.1.1, 11.2.2.1, Vol. 1.52, pp. 7-7102, 7-7105

As shown in the above table, no statistically significant differences were found between the two treatment arms with respect to demographics or the baseline characteristics of the actinic keratosis lesions.

Evaluability by Center/Investigator: ALA-018

	LEVULAN®				Vehicle			
	First Treatment			Second Treatment	First Treatment			Second Treatment
Investigator	Enrolled	ITT *	Evaluated at Week 8	Received/ Eligible#	Enrolled	ITT*	Evaluated at Week 8	Received/ Eligible#
M.G. MERCURIO/ SCHER New York, NY U.S.A.	4	4	4	2/2	0	0	0	0
S.D. GLAZER Buffalo Grove, IL U.S.A.	18	18	18	5/5	6	6	6	6/6
M. LING Atlanta, GA U.S.A.	18	18	18	2/3	6	6	5	5/5
D.J. PIACQUADIO San Diego, CA U.S.A.	5	5	5	3/3♦	2	2	2	2/2
J.R. TAYLOR Miami, FL U.S.A.	15	15✡	13	6/6	5	5	5	3/3
S.E. WHITMORE Baltimore, MD U.S.A.	8	8	8	2/2	2	2	2	2/2
J. GOODMAN West Palm Beach, FL U.S.A.	13	13	13	5/5	5	5	5	4/4
H. FARBER Philadelphia, PA U.S.A.	7	7	7	0/0	3	3	3	1/2

*ITT: patients who are enrolled, randomized, and who receive LEVULAN® or vehicle at first treatment

#Received/Eligible: Of patients known to have persistent target lesions at week 8, number who receive LEVULAN® or vehicle treatment at week 8

♦One patient (18402) received drug at retreatment but did not return for light retreatment

✡One patient (18517) received drug but did not return for light treatment

Sources: Vol. 1.52, Table 6.1 (pg. 7-7069) and Table 10.1.1, pg. 7-7094, Data Listing 7

Reviewer's Comment:
There are different blinded and unblinded investigators at each site. Seven of the centers had unblinded investigators who were not physicians; one center had one unblinded investigator who was a physician, and one who was not a physician.
The unblinded investigators were responsible for collecting safety data [erythema, edema, signs/symptoms of phototoxicity or adverse events] in this study. The quality of

the safety data is rendered suspect because most of the unblinded investigators are not physicians. (At the time of completion of this review, medical officer has not been supplied with information about the qualifications of the unblinded investigators). For Phase 4 studies to collect additional safety data, Agency should specify that both unblinded and blinded investigators are physicians.

8.3.1.4.2 Efficacy

8.3.1.4.2.1 Primary Efficacy Results

The following table depicts Agency and Sponsor analysis of the fraction of patients in each treatment arm for whom all target lesions completely resolve at week 8 after treatment.

Response Rates at Week 8, ITT, L.O.C.F.: ALA-018

	Sponsor Analysis: 100% Complete Response Rate (Tables 22.5, 22.6, 22.7)				Agency Analysis: 100% Complete Response Rate			
	Active	Vehicle	95% Confidence Interval of difference	p-value	Active	Vehicle	95% Confidence Interval of difference	p-value
Total	60/87 (69%)	4/29 (14%)	39%-71%	<.001	60/88* (68%)	4/29 (14%)	39%-71%	<.001
Face	49/71 (69%)	2/21 (10%)	43%-76%	<.001	49/72^ (68%)	2/21 (10%)	43%-76%	<.001
Scalp	11/16 (69%)	2/8 (25%)	6%-81%	.099	11/16 (69%)	2/8 (25%)	6%-81%	.099

*Denominator was changed from 87 to 88 in the Agency ITT analysis. Patient 18517 is excluded from sponsor's L.O.C.F. analysis because of withdrawal from study after less than 500 seconds of light. Though there is no efficacy data on this patient, the patient should be included in ITT analysis. Changing the denominator from 87 to 88 has a negligible effect on treatment outcome.
This ratio differs slightly from that calculated by the statistical reviewer (59/88) because medical reviewer has not excluded from the count of cleared patients #18508, who achieved 100% CR at week 4, and was then lost to follow-up.

^Denominator was changed from 71 to 72, for same reason as listed above.

The noteworthy information to be extracted from this table includes:

(1) PATIENTS WITH FACE LESIONS: outcomes of patients treated with LEVULAN® and blue light were significantly superior to outcomes of patients treated with vehicle and blue light;

(2) PATIENTS WITH SCALP LESIONS: (a) outcomes of patients with scalp lesions treated with LEVULAN® and blue light were similar to those of patients with facial lesions treated with LEVULAN® and blue light, and (b)

outcomes of patients with scalp lesions treated with LEVULAN® and blue light trended to superiority compared to outcomes of patients with scalp lesions treated with vehicle and blue light (the difference was not statistically significant, probably because there were an insufficient number of enrolled patients with scalp lesions);

(3) ALL PATIENTS: outcomes of patients treated with LEVULAN® and blue light were significantly superior to outcomes of patients treated with vehicle and blue light. .

100% CR Rate at Week 8 by Center/Investigator: ALA-018		
Investigator	LEVULAN®	Vehicle
M.G. MERCURIO/ SCHER New York, NY U.S.A.	1/4 (25%)	0/6
S.D. GLAZER Buffalo Grove, IL U.S.A.	13/18 (72%)	0/6
M. LING Atlanta, GA U.S.A.	15/18 (83%)	0/6
D.J. PIACQUADIO San Diego, CA U.S.A.	2/5 (40%)	0/2
J.R. TAYLOR Miami, FL U.S.A.	8/15 (53%)	2/5 (40%)
S.E. WHITMORE Baltimore, MD U.S.A.	6/8 (75%)	0/2
J. GOODMAN West Palm Beach, FL U.S.A.	8/13 (62%)	1/5 (20%)
H. FARBER Philadelphia, PA U.S.A.	7/7 (!00%)	1/3 (33%)

If the outlier center (Dr. Farber's) were excluded from analysis, the overall 100% CR rate would decrease from 68% to 65%, which is not a substantial change.

A treatment for actinic keratoses that results in temporary disappearance, but not permanent destruction, of these lesions has little clinical utility. The study was designed such that no patient was followed for longer than 12 weeks after the first treatment, making it impossible to confirm that cleared lesions did not recur during a longer follow-up. However, it is reassuring to note (as is depicted in the following table) that among patients who had achieved 100% complete response by week 8, the vast majority remained clear of all their target lesions at week 12.

Remission Duration in Patients with 100% CR Observed at Week 8: ALA-018

Among patients with 100% CR rate observed at Week 8*	LEVULAN(%)(N=59✻)
100% CR MAINTAINED AT WEEK 12	55 (93%)
100% CR LOST AT WEEK 12	4 (7%)[3 of the patients (18111, 18406, and 18114) had facial lesions recurring, 1 (18606) had scalp lesions recurring]
*The 100% CR rate observed at Week 8 was either achieved at Week 4 and maintained, or achieved at Week 8	
✻The number of cleared patients counted in this table (59) is less than that counted in preceding table (60), because this table excludes patient 18508, who was lost to follow-up prior to week 12.	

Those subjects with any persistent target lesions at Week 8 were eligible for retreatment of those lesions at that time, following the same randomization scheme as in the original application. As depicted in the following table, evaluating the population of all patients, and the subset of patients with facial lesions, repeat treatment of persistent target lesions with LEVULAN®/blue light converted significantly more patients to 100% complete responses by week 12 than did repeat treatment with vehicle/blue light. For the subset of patients with persistent scalp lesions, retreatment with LEVULAN®/blue light trended toward a benefit, but the difference was not statistically significant (likely due to the small numbers of retreated patients).

Among Patients with Lesions Retreated at Week 8, Patients with 100% CR Rate at Week 12: ALA-018

	LEVULAN®	Vehicle	95% Confidence Interval of difference	p-value
Total	15/25 (60%)	0/23 (0%)	41%-79%	<.001
Face	13/21 (62%)	0/17 (0%)	41%-83%	<.001
Scalp	2/4 (50%)	0/6 (0%)	1%-99%	.317
Sources: Table 24.4, 24.5, and 24.6				

The phototoxic effect of LEVULAN® is contingent upon the drug penetrating through the stratum corneum and into the living part of the epidermis. One potential concern about the clinical utility of LEVULAN® for treatment of actinic keratoses is whether LEVULAN® is as effectual for thicker lesions. (Of note, very thick and/or

hyperkeratotic actinic keratoses were specifically excluded from being chosen as target lesions, presumably because of sponsor's concern that these lesions would not susceptible to treatment with LEVULAN®/blue light). The following table compares the **lesion** clearance rate for different lesion grades (outcomes for lesions of the same grade located on face and scalp are pooled for this analysis).

Lesion Complete Response Rate at Week 8, L.O.C.F. for different Lesion Grades: ALA-018

	LEVULAN®	Vehicle	95% Confidence Interval of Difference	p-value
Lesion Grade 1 (lesions are slightly palpable, and better felt than seen)	300/327 (92%)	41/115 (36%)	47%-65%	<.001
Lesion Grade 2 (lesions are moderately thick actinic keratoses, easily seen and felt)	213/273 (78%)	28/88 (32%)	35%-57%	<.001
Source: Tables 18.5, 18.6				

While the active treatment outcomes are significantly superior to those of vehicle treatment for each lesion grade, the complete response rate decreases as lesion grade increases. The difference between the complete response rates for the different lesion grades is statistically significant.

8.3.1.4.2.2 Secondary Efficacy Results

The protocol-specified secondary efficacy variables included investigator's cosmetic evaluation of each treated lesion (at weeks 4, 8, and 12), patient's self-evaluation of their overall response (at week 12), and patient assessment at week 12 of the acceptability of the therapy compared to other prior therapies for actinic keratoses. Grading of cosmetic response of treated lesions and of overall response was in four categories: excellent, good, fair, and poor.

Cosmetic Evaluation of Lesion by Blinded Investigator, Week 12: ALA-018

Cosmetic Scale	LEVULAN®	Vehicle
Excellent	466 (80%)	60 (30%)
Good	82 (14%)	14 (7%)
Fair	14 (2%)	18 (9%)
Poor	18 (3%)	107 (54%)
Total	580	199
P value<.001 (Cochran-Mantel-Haenszel mean score test (RIDIT scores)		
Source: Table 11.4.1.7.1.1		

Reviewer's Comment: The way these categories are defined permits investigator to capture in one grading scale (a) whether treatment has resolved a lesion, and (b) whether lesion resolution is accompanied by a cosmetically acceptable appearance. It is impossible to tease from the cosmetic evaluations the relative weights of these two effects in determining the "cosmetic" grade. That better "cosmetic" responses are observed following LEVULAN® treatment than vehicle treatment may reflect the higher likelihood of lesion cure following LEVULAN® treatment, and not necessarily reflect aesthetically satisfactory outcomes with LEVULAN® treatment.

8.3.1.5 Safety

8.3.1.5.1 Extent of Exposure

62 subjects received one treatment of LEVULAN®/blue light, 25 subjects received two treatments of LEVULAN®/blue light, and one subject received one treatment of LEVULAN® without blue light.

8.3.1.5.2 Discontinuations

No subjects were permanently or temporarily discontinued from the study due to laboratory abnormalities. Two patients, both enrolled in the LEVULAN® arm discontinued due to adverse events experienced during the light treatment. One discontinued (at Baseline Visit B) because of a complaint about heat. The other patient discontinued during retreatment of persistent target lesions at week 8, but the reason for the discontinuation was not specified.

8.3.1.5.3 Adverse Events(Sponsor's Assessment)

Local cutaneous adverse events will be reported separately. Sponsor reports that 31 patients on active treatment and 12 patients receiving vehicle treatment experienced adverse events during this study. Sponsor's table below lists the number of patients with